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ABSORPTION OF INHALED REACTIVE GASES

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16. ABSTRACT

In inhalation toxicology an important concept involves the determination of dose as a major component for providing a perspective to judge the applicability of various toxicological results to human exposure conditions. This chapter reviewed some of the biological, physical, and chemical factors that affect dose and that must be understood to interpret experimental toxicological data and to develop theoretical dosimetry models. Dosimetry experiments involving laboratory animals and humans were briefly discussed, showing the variability in uptake according to the reactive gas, animal species, and respiratory tract region. The results of theoretical dosimetry models were illustrated showing the effects on predictions due to different inter- and intraspecies LRT anatomical models, due to different TB liquid lining thicknesses, and due to the chemical rate constant of the liquid lining of the TB region. Also illustrated was the use of predictions for interspecies dosimetry comparisons by comparing the dose profiles of rat, guinea pig, rabbit and human. In spite of the complexities involved in experimental or theoretical dosimetry, results so far illustrate the feasibility of making interspecies LRT dosimetry comparisons for evaluating the toxicity of inhaled toxic gases, of providing sensitivity studies to determine processes and parameters needing additional research, and of assisting in experimental design.

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INTRODUCTION

Dosimetry is an integral component of hazard evaluation for inhaled chemicals. In making interspecies comparisons of toxicological results, dosimetry data allows concentration-response data to be evaluated with respect to dose-response relationships. Thus, knowledge of interspecies differences in dosimetry is critical to the overall risk assessment process.

It should be noted that dosimetry refers to estimating or measuring the amount of a chemical reaching various target sites. Both experimental and theoretical studies are employed in obtaining absorption data for specific chemicals. In this chapter we discuss the uptake of highly reactive gases in the respiratory tract, with emphasis on the physical, chemical and biological factors involved in absorption and on examples of results of theoretical and experimental dosimetry investigations. The reader is referred elsewhere for treatments of insoluble particles (Raabe, 1979; Stewart, 1984; U.S. EPA, 1982), hygroscopic particles (Martonen, 1982; Martonen et al., 1985), and soluble but non-reactive gases (Fiserova - Bergerova, 1983).

First discussed are the factors and processes that affect the absorption of reactive gaes, including the morphological and structural aspects, and the physical and chemical factors involved. The factors discussed are biochemical composition, chemical reactions, solubility, molecular diffusion, and convection in respiratory tract fluids. For a discussion of transport in the lumens of the airways and airspaces see Overton (1984). Following this is a brief summary of dosimetry experiments involving the uptake of either formaldehyde, ozone or nitrogen dioxide by laboratory animals and humans. Finally, theoretical dosimetry predictions are considered.

Here we present illustrations of the predicted uptake and distribution of O_3 in the lower respiratory tract (LRT) of man and laboratory animals that resulted from using the model of Miller et al. (1985) and Overton et al. (1987a). The discussion illustrates how theoretical models can be used to explore the effects on predictions due to the values of various parameters that characterize the respiratory tract of an animal or species. Also illustrated is the use of predictions for inter- and intraspecies dosimetry comparisons. For a discussion of the specific mathematical dosimetry model formulation see the above references as well as Miller et al. (1987a,b) and Overton et al. (1987b).

FACTORS AND PROCESSES AFFECTING ABSORPTION

Major factors affecting the local uptake of a reactive gas in the respiratory tract (RT) are RT morphology and anatomy, the route of breathing (nasal, oral, oronasal), the depth and rate of breathing, the physicochemical properties of the gas, the processes of gas transport, and the physicochemical properties of the liquid lining of the lung, lung tissue, and capillary blood. These factors and processes interact in a complex way and need to be considered in developing theoretical dosimetry models and interpreting experimental data.

Morphological Aspects

Figure 1 illustrates some of the important aspects of lower respiratory tract (LRT) structures and their relationship to concepts used in modeling. Figures 1a-1c present the relevant morphological and anatomical features of the LRT; whereas, Figures 1d and 1e illustrate a specific model representation of the features. Figure 1a shows a representation, developed by Weibel (1963), of the structure of the

airways of the tracheobronchial (TB; region distal to but including trachea) region and of the ducts and sacs of the pulmonary region of the human lung. For mathematical modeling, the respiratory tract can be conceived of as a series of sets of right circular cylinders (see Figure 2). Although very simplistic, anatomical models of this type have been found to be useful for simulating the absorption of gases as well as of aerosols. Data are needed on the lengths, diameters, and the number of cylinders (that represent the lumens of the airways, ducts or sacs) in each generation or set. In the pulmonary region, data on the number of alveoli, their surface area and volume are also needed. Table 1 illustrates a typical anatomical model.

In the upper respiratory tract (URT; region proximal to trachea) and in the TB region, the mucociliary layer protects the tissue from direct exposure to the inhaled gas. This layer is composed of an epiphase and an underlying hypophase (Figure 1c). The epiphase is a highly viscuous mucous layer of varying thickness and may not be continuous. At present this is an area in which most of the available data is from animal studies. Table 2 gives an indication of some of the thickness data, including animal species studied, location in the respiratory tract where measurements were made, thickness, and relevant comments by the investigators. For man, data are very limited and assumptions about the thickness of the liquid lining must be made, often based on non-human data.

The hypophase is made up of a watery fluid, 4 to 7 um thick, in which cilia move back and forth in a manner that propels the mucus to the glottis where it is removed from the respiratory tract along with any collected contaminants on its surface or imbedded within. This process

is called mucociliary clearance and is an important RT defense mechanism.

For irreversible and highly reactive gases, such as O_3, penetration to capillary blood in the URT and TB regions can be ignored (Miller et al., 1985). Figure 1e illustrates the model compartment concept for this case as well as for the case for which the two liquid phases are assumed indistinguishable. For highly soluble or slowly reacting gases a blood compartment as well as the consideration of other body organs and compartments may be necessary.

The major features of the pulmonary fluids and tissue structures are illustrated in Figure 1b. The epithelium is made up predominantly of two types of cells, called Type I and Type II. The first type of cell is identified with the process of respiration; it covers over 95% of the alveolar surface area. Type II cells have metabolic and secretory functions as well as being involved in the repair of damage. A thin liquid film separates the epithelial cells from the air over much of the pulmonary surface area; its thickness is highly variable from .01 to several microns thick with an average of about 4% of the air-barrier thickness (Weibel, 1973). Below the epithelial layer are the interstitium and the wall of the capillaries, the endothelial cells. A simple model formulation for the pulmonary tissue/fluid structure is shown in Figure 1d. Along with liquid lining thicknesses, estimates of tissue and capillary blood compartment thicknesses are also required. Table 3 gives an indication of the type of data available for defining pulmonary tissue and capillary blood compartment dimensions needed in dosimetry models.

Physical and Chemical Aspects

So far we have been concerned about RT structure and the data necessary to describe the physical dimensions of the airways, ducts, sacs, and alveoli, and of the liquid lining,tissue and capillary blood compartments. It is within these defined dimensions that the transport of gases occurs and that the chemical reactions of toxic gases with biochemical constituents take place that may result in toxic effects. Thus, information that characterizes these processes is needed for mathematical models. Specifically, in the air phase or air compartment (airway lumens and air spaces), the processes of convection, molecular diffusion, turbulence, dispersion, and the loss or gain of gaseous species to and from the RT walls must be taken into account. The major factors to be considered in lung fluids and tissues include the biochemical constituents of lung tissues and fluids, chemical reactions, solubility, molecular diffusion, convection due to mucociliary action and capillary blood flow. Transport in the air phase will not be discussed here as it is beyond the scope of this chapter. The reader is refered to Overton (1984) for a summary of this topic.

The Chemical Composition of RT Fluids and Tissues

Much of what is known about the chemical composition of the liquid lining of the TB region comes from lavage data on patients with pulmonary diseases such as cystic fibrosis, asthma, and chronic bronchitis. Although data have been obtained recently from patients without lung problems (e.g., Woodward, 1982), techniques are still needed to collect the pericilliary fluid, as present approaches recover mostly the mucus of the epiphase (Boat and Cheng, 1980). Lavage fluid

is separated into two components,the unsoluble constituents called gel and the solubles in the sol portion. Mucus (gel) has four major constituents: lipids (0.3%-0.5%), glycoprotein (2-3%),proteins (0.1-0.5%), and water (95%) (Lopez-Vidriero and Reid, 1980). However, the constituents may have been modified from those of healthy persons due to disease. The wattery substance (sol) may or may not be chemically similar to the periciliary fluid.

Some of the major unsaturated fatty acids (UFA) and amino acids (AA), and their concentrations, found in the constituents of lavage fluids, as well as other lung fluids and tissue, are listed in Tables 4 and 5. These materials can be the target of toxic gases; for example, both O_3 and NO_2 react with UFAs, and O_3 also reacts with amino acids. The values in the tables are calculated using reference data.

Data on the chemical make up of the liquid lining of the pulmonary region comes mainly from analysis of the insoluble fraction of pulmonary lavage material. The soluble portion that may correspond to the hypophase or serous fluid is seldom analyzed. The insoluble component, corresponding to the monolayer of surfactant material, is 10% to 20% protein, 1% to 2% carbohydrates, and 80% to 90% lipid (Sahu and Lynn, 1977). Tables 4 and 5 also list some of the UFA and AA components of the insoluble part of pulmonary lavage fluid and their estimated concentrations . The serous fluid, because of its greater thickness, probably has more influence on gas absorption than the thinner surfactant layer.

The chemical composition of blood and tissue is not much different than that of the liquid lining, mainly water with traces of lipids, glycoproteins, and proteins, and smaller molecules. However, the concentrations of the molecular components of the major constituents of

blood and tissue are very different (see Tables 4 and 5). There is a considerable range in the concentration values of the different fatty acids (Table 4) and amino acids (Table 5) for the various tissues and fluids illustrated.

Chemical Reactions

Chemical reactions occur as a result of the collision of molecules. The molecules that collide (reactants) merge and then break up into one or more molecules (products) that may or may not be different from the reactants. Reactions are often classified by "order", such as first order, second order, third order, etc., indicating that the rate of the reaction is proportional to the product of the concentrations of the species involved. By rate of reaction is meant the rate of loss of one of the reactants (e.g., moles per liter per second), and in many cases, it is also equivalent to the rate of production of the products. For example, if the reaction is first order, then the rate of loss of species A is given by, rate = k_1 [A]; where [A] is the concentration of species A, and k_1 is the first order rate constant. If [A] and [B] are the concentrations of reacting species A and B, respectively, then the reaction is second order if the rate of loss of one of the species is given by, rate = k_2 [A][B]. The constant of proportionality, k_2, is the second order rate constant. In general, however, rate expressions can be more complex and may involve concentration values taken to a non-integer power. Rate expressions can be obtained from theoretical considerations or based on experimental data.

Theoretically, knowledge of all of the chemical species involved, the reaction rates of the reactants, and of the products are needed to

characterize a reacting system for modeling purposes. In practice, however, complete information is not always available; even if reaction rates are known, the products and their formation rates may not be available. This may not be a problem if the products are not of interest and do not react significantly with the known reactants.

There is extensive theoretical and experimental information on the absorption and chemical reaction of gases in thin films (e.g., Danckwerts, 1970; Sherwood et al., 1975; and Astarita, 1967) that is applicable to the thin layers of the liquid lining, tissues, and capillaries of the lung. Many of the theoretical works deal with techniques for solving problems of complex chemical systems. Sometimes the complexities can be reduced by the fact that reactions can be classified as either slow, fast, or instantaneous, depending upon the system. Obviously the classification is relative; however, for each of these types, there are approximation techniques that may be used to simplify procedures for calculating the time and spatial dependence of interacting compounds. Ways of treating complex interacting systems are discussed in Danckwerts (1970) and Astarita (1967), among others.

The chemistry of absorbed gases in water is important, not only because 85-95% of the main constituent of lung fluids and tissues is water, but also because many toxic species react with water, affecting the absorption rate, as well as creating products that may be important in further reactions with the absorbed gases and the biological constituents. NO_2, O_3, NH_3, SO_2 and CO_2 are common in the atmosphere, and react with, as well as interact in water (see Durham et al., 1981, 1984) giving rise to bisulfite, nitrite, nitrate, and sulfate molecules, and the potential for lowering pH, all of which could have an or indirect adverse effect

on lung tissues and fluids.

Examples of some of the water reactions are given in Table 6. Notice how the reactions of the carbon, sulfur and nitrogen compounds are interrelated by the hydrogen ion. In addition, O_3 oxidizes both nitrogen and sulfur species. With the introduction of biochemical constituents, the reacting system will become more complex. However, depending on conditions, some of these reactions will be more important than others. For example, reactions 6, 11 and 14-17 in Table 6 will be competing with the reactions of O_3 and NO_2 with organic biochemical compounds. Most probably (at least for an initial exposure when the concentration of reacting organic molecules have not been depleted), the reactions of NO_2 and O_3 with the organic compounds are the more important (Postlethwait and Mustafa, 1981) and reactions 6, 11 and 14-17 can be omitted from the reaction scheme. However, the reactions of SO_2 with water (reactions 4 and 5, Table 6) probably cannot be neglected. At normal pH levels of the liquid lining (~7) the equilibrium concentration of HSO_3^- is over 100 times the liquid phase concentration of SO_2. In other words, most of the absorbed SO_2 is rapidly transformed to HSO_3^- and SO_3^{2-} resulting in a much larger mass transfer coefficient than without the chemical reactions. In addition, reactions 4 and 5 are needed to handle the (known) desorption of SO_2. If necessary, the important reactions can be determined by chemical kinetic modeling to gain information that will allow simplifying the system (by keeping only the important reactions) for use in dosimetry modeling.

According to Menzel (1976), the most toxic of oxidizing air pollutants is ozone, its oxidative properties being responsible for its toxicity. Thus, as an example of the type of reactions of a toxic gas with biochemical

constituents that may have to be considered in developing a dosimetry model, the reactions of O_3 are briefly outlined. Even though O_3 reacts with almost all classes of biological substances, physiological, morphological, and biochemical effects of O_3 point to cellular membranes as the likely site of toxicity (Menzel, 1984), suggesting lipids as the major target. Olefins are very sensitive to O_3; the mechanism of reaction is the Criegee mechanism (Pryor et al., 1983) in which O_3 attacks the carbon double bond in the UFA. Other mechanisms are also involved in which toxic free radicals are produced that can cause damage; however, the Criegee process is considered the main reaction path for most O_3/UFA reactions (Pryor et al.,1983).

Rate constants for the reaction of O_3 with some biological UFAs are known (e.g., Razumovskii and Zaikov, 1972); nevertheless, for most biological substances, rate constants *in vivo* are lacking. For example, the degree to which O_3 is able to penetrate membranes and react with the double bonds on UFAs in lipids is unknown (Pryor et al., 1983).

According to Pryor et al. (1983), ozone also reacts with amino acids, proteins and sugars. In water the only AAs found to react with O_3 are (in order of increasing reactivity): phenylalanine, cystine, hystidine, tyrosine, tryptophan or methionine, and cysteine. The mechanisms for damage to proteins are not well known; but a non-radical Criegee process is possible, and there is evidence for a radical path. Sugar reactions are expected to be slow; however, the reaction of O_3 with sugars, as well as with nucleic acid, has not been studied. Vitamin E is known to protect both UFAs and lung tissue aganist some of the effects of O_3 by scavaging radicals; even so, this vitamin does not interfere with the non-radical Criegee process.

Solubility

The ability of a medium, such as water, blood, mucus, or tissue, to absorb a gas is called solubility. The more soluble a gas the greater the quantity of that gas absorbed than is the quantity of a lesser soluble gas in similar circumstances. There are many different expressions for the solubility of gases, including Ostwald's, Bunsens's, Kuenen's and Henry's law (Clever and Battino,1975). The expressions differ in terms of units as well as in the definition of what chemical form of the gaseous species in the liquid phase is related to gas phase quantities. In general, the air and liquid phase quantities of the gas are defined as being proportional in conditions of equilibrium; the "constant" of proportionality characterizes the particular system. For example, the Bunsen's absorption coefficient is defined as the volume of gas at standard temperature and pressure dissolved by unit volume of a liquid when the partial pressure of the gas is one atmosphere. Chemical reactions may or may not be involved; thus, Bunsen's coefficient not only accounts for total absorption, but its value also depends on the properties of chemical reactions, if any.

On the other hand as long as the concentration of dissolved gas is small and the pressure and temperature is not close to the critical pressure and temperature, then Henry's law is obeyed. This formulation applies only to the uncombined or free form of the gas in solution; thus it does not account for all of the absorbed gas. However, Henry's law constant is independent of chemical reactions and can be used in quantifying the concentration of the molecular form of a gas in solution which maybe involved in chemical reactions. This law can be expressed

in several different, but equivalent, forms for the same gas and liquid, a convenient form being, $C_g = HC_l$. C_g and C_l are the gas and liquid phase concentrations, respectively. H is Henry's law constant and it is the ratio at equilibrium of the gas phase concentration to the liquid phase concentration of the gas (e.g., moles per liter in air/moles per liter in solution). In general, the constant is a function of temperature and the molecular properties of the liquid and the gas; however, for constant temperature and the ranges of ambient concentrations of toxic gases, the coefficient can be considered constant and is applicable to biological systems.

Henry's law is not restricted to gases alone but applies to dilute solutions of solids or liquids in liquids and can be extended to gases in equilibrium in two immiscible liquids with a common interface; but more importantly, it is applicable to "layers" of biological fluids and tissues. In this situation, the ratio at equilibrium of the concentrations in the two phases or layers is the ratio of the Henry's law constant of the air/solution system of one phase to the Henry's law constant of the air/solution system of the other phase. This ratio is called the distribution coefficient or the partition coefficient.

Table 7 is a list of gases and Henry's law constants for water. The gases are listed with the values of the constants decreasing downward, with increasing solubility -- if there were no chemical reactions involved. This means that Henry's law constant relates the molecular form of the gas in water and air and not the total quanity absorbed in water to air quantities. Thus, as defined in this latter sense, the relative solubilities of the gases in Table 7 may be different

than implied by the order. (An example of the effect of chemical reactions on the absorption of SO_2 is discussed in the section on chemical reactions)

By studying Table 8, a collection of Henry's law constants for several gases in biological fluids and tissues, we see for the small molecules listed that there is not much variation for Henry's Law constant among the various substances for a given gas. Except for C_2H_4 the use of the water value would seem justifiable. Although Table 8 is incomplete, it suggests that the value of H is not influenced much by different biological tissues and liquids, suggesting that a known value for one tissue or liquid is a reasonable approximation for missing values.

A list of partition coefficients for small molecule gases with several biological tissues and fluids is given by Altman and Dittmer (1971). The values are close to one suggesting that animal fluids and tissues are very similar as far as solubility of gases of small molecules is concerned--further supporting the conclusion in the above paragraph. However, this does not hold in general for the gaseous organic compounds and extrapolation from water data to biological fluids and tissues is not always appropriate.

Molecular Diffusion

Molecular diffusion is a process that redistributes molecules in such a way that there is a net flow of the molecules from regions of high concentration to regions of lower concentration (Danckwerts, 1970). Diffusion also can result because of temperature or pressure gradients, external electrical fields, and potentials (Sherwood et al., 1975). Often the term "driving force" is used in connection with diffusion. According to Danckwerts, however, the molecules do not experience a net

force in the direction of flow; only the random collisions of the molecules are responsible for the process.

The flux, F, or the net rate of transfer of mass or of the number of specific molecules across a plane perpendicular to a given direction due to molecular diffusion is defined as $F=-D\ (dc/dx)$. In this equation, known as Fick's law, dc/dx is the concentration gradient along the given direction and D is the molecular diffusion coefficient, defined by the above equation.

The value of the diffusion coefficient depends on the properties of the gas molecule and the medium. Although, the effect of polymers on diffusion follows no simple pattern, the diffusion coefficient of small molecules, such as O_2 and CO_2, in solutions of biological proteins is approximately the same as in polymer solutions (Sherwood et al., 1975; Navari et al., 1971). Thus, the diffusion coefficients of small molecules in dilute polymer solutions, with constituents similiar to those in biological fluids and tissues, are probably similar to, but smaller than, the value in pure water. For small molecules, other than O_2 and CO_2, such as O_3 and NO_2 this conclusion probably is reasonable. For the larger gaseous and organic molecules, diffusion coefficients in biological substances may be very different than the pure water values, making measurements in biological tissues and fluids necessary.

Values for the molecular diffusion coefficient of a few gases in biological fluid and tissues have been measured. The values are generally less than in water. According to Altman and Dittmer (1971), for example, the values for O_2 in water, ox serum, frog muscle, dog connective tissue, and rat lung tissue are, $3 \times 10\text{-}5$, $1.7 \times 10\text{-}5$, $1.2 \times 10\text{-}5$, $.97 \times 10\text{-}5$, and $2.3 \times 10\text{-}5$ cm^2/sec, respectively.

Bulk Flow or Convection in Lung Fluids

The liquid lining of the URT and TB regions, and capillary blood are in motion. This motion or flow is such that absorbed gases can be redistributed in the RT or even transported to non-lung organs and compartments to be lost from the RT or possibly to be returned. In addition, depleted biochemical compounds can be replinished by the flow process. The extent of the redistribution depends on the particular flowing system and the reactive gas. For example, Miller et al. (1985) estimated that for O_3, an irreversible reacting and highly reactive gas, that pulmonary capillary blood flow rates and TB liquid lining or mucous flow rates are too slow to affect O_3 absorption.

To be able to account for liquid flow or convection (in modeling) the rates of flow (e.g., volume of liquid per unit time) of the fluids are needed. Mucous flow rates in the URT (e.g., Proctor, 1982; Morgan et al.,1984) and the larger airways of the TB region (e.g., Iravani and van As, 1972; Yeates et al., 1975; Wolf and Muggenburg, 1979; Felicetti et al.,1981) are available for several species. Iravani and van As (1972) reported rates in the smaller airways. In addition, estimates of rates in all airways have been made based on clearance data from selected airways, anatomical data, and other assumptions (e.g., van As, 1977; Miller et al.,1978). For example, transport rates in each airway generation of guinea pigs were estimated by Velasquez and Morrow (1984) by applying kinetic equations to data on particle retention in five airway zones (based on airway diameter). The estimated mucociliary (particle) rates ranged from approximately 8 mm/min in the trachea to 0.001 mm/min in the distal bronchioles. However, mucociliary rates are not necessarily the same as the liquid lining bulk or convective flow

rates and further data or assumptions must be used to estimate convection velocities. Nevertheless, the estimated rates are probably a good first approximation.

Pulmonary capillary blood flows have been measured (e.g., Horimoto et al., 1981; Wagner et al., 1982), as well as theoretically calculated (e.g., Overholser et al., 1981; Zhuang et al., 1983). Because the distance from the air to capilaries in the TB region is at least 7 to 20 times as great as it is in the pulmonary region, highly, but irreversable, reacting gases such as O_3 will not reach the capillaries proximal to the pulmonary region (Miller et al., 1985). However, Heck et al., (1983) demonstrated that either HCHO or (most probably) its reaction products were transferred to extrapulmonary tissues and fluids outside the URT. Also, NO_2 products are known to be transferred out of the lung (Goldstein et al., 1985; Postlethwait and Mustafa, 1981). Most probably, TB or pulmonary region capillary blood flow is a major factor in the transfer. Thus, in developing dosimetry models, the effect on gas absorption by product removal from the lung (and by re-introduction into the RT) by blood flow should be considered to determine their importance.

ABSORPTION IN EXPERIMENTAL ANIMALS AND HUMANS

For discussion, we have chosen experiments involving HCHO, O_3 and NO_2.

Upper Respiratory Tract Experiments

Formaldehyde

Egle (1972) measured the upper respiratory tract uptake of HCHO in dogs. For the two-way experiment in which air was passed through the URT "in a manner as to represent both inhalation and exhalation" (Egle, 1972a), 100% of the HCHO was retained at all flow rates. In the one

way experiments (simulating inhalation) the uptake increased from 95% to 100%, with increasing flow rate.

The investigation of Heck et al., (1983) was concerned with the distribution of inhaled $H^{14}CHO$ in different tissues and fluids of rats. The highest concentrations of radioactivity were observed in the nasal mucosa of the URT. Radioactivity was also detected in lung tissue, as well as in non-lung tissue, indicating rapid transfer of $H^{14}CHO$ or reaction products out of the respiratory tract. For the six hour exposure the amount absorbed was found to be approximately proportional to the air concentration.

Swenberg et al. (1983) used $H^{14}CHO$ and autoradiography to locate the regions of high deposition in the URTs of rats and mice. They found heavy deposition of radioactivity in the anterior nasal cavities, correlating well with observed lesions in similarly exposed animals. Heavy deposition was also found in the ventral portion of the cavity where significantly fewer tumors have been found. This region is lined with squamous epithelium, suggesting less sensitivity of this type of epithelium to HCHO compared to respiratory epithelium. A whole body autoradiograph showed heavy deposition of radioactivity in the nasal cavity and in the anterior half of the trachea. Moderate amounts were deposited in the bronchi. Autoradiography, combined with densitometry, may be useful in determining the relative amounts of radioactivity in different areas or locations of the URT and in the major airways of the LRT.

Ozone

The isolated upper airways of beagle dogs were exposed to O_3 at a continuous flow of 3.0 l/min by Vaughan et al., (1969). For concentrations of 0.2 to 0.4 ppm, one-hundred percent uptake by the

nasopharyngeal region was reported. Yokoyama and Frank (1972) observed 72 percent uptake at 0.26 to 0.34 ppm (3.5 l/min to 6.5 l/min flow rate) using a different procedure. Replicating the procedure of Vaughan et al., (1969), Yokoyama and Frank (1972) found that 03 was absorbed on the wall of the mylar bag used in collecting the gas below the trachea, suggesting that the 100% uptake results of Vaughan et al., were due to experimental artifacts. Interestingly, if only the data for the inspired concentrations from 1 ppm to 9 ppm in the figure in Vaughan et al., (1969) are considered, then the uptake is 60% to 70%, in keeping with the values reported by Yokoyama and Frank (1972) for the much lower concentrations.

Yokoyama and Frank (1972) also observed a decrease in the percent uptake due to increased O_3 concentration and due to increased flow. With nasal breathing at approximately 0.3 ppm O_3, the uptake decreased from 72 percent to 37 percent for a flow rate increase from 5 to 40 l/min. An increase in concentration from 0.3 ppm to 0.79 ppm decreased nasal breathing uptake (at 5 l/min) from 72 percent to 60 percent. Their data also indicate that tracheal concentrations increased with increasing oral or nasal concentrations. Also demonstrated was the fact the percent uptake as well as the concentrations of O_3 reaching the trachea depended heavily on the route of breathing. For a given flow rate, nasal uptake significantly exceeded oral uptake.

The loss of O_3 in the URT of acutely and chronically exposed dogs was investigated by Moorman et al., (1973). Chronically exposed (18 months) to 1 to 3 ppm of O_3 beagle dogs under various daily exposure regimes had significantly higher tracheal O_3 concentrations than animals

tested after one day of exposure to similar regimes. The authors suggested that the differences were due to physiochemical changes of the mucosal lining of the chronically exposed animals. Additionally, dogs exposed for 18 months to 1 ppm for 8 hours per day exhibited lower tracheal concentrations than those continuously exposed. However, according to EPA (1978), when the insensitivity of the O_3 monitor used to measure the responses is taken into account the average tracheal concentration of the acutely and chronically exposed animals are not significantly different. Thus, at the levels of exposure used in the experiment there is no evidence that chronic exposure would result in lower tracheal concentrations than acutely exposed animals.

Miller et al. (1979) studied the nasopharyngeal removal of O_3 in rabbits and guinea pigs over a concentration range of 0.1 ppm to 2.0 ppm. The O_3 concentration in the trachea in the two species was found to be similar for the same inhaled concentration, the tracheal concentration being linearly related to the chamber concentration that was drawn through the isolated upper airways. Ozone removal in both species was approximately 50 percent.

Gerrity et al., (1987) inserted a small polyethylene tube into the nose of human subjects (seated in a chamber into which O_3 was introduced) so that the tip was positioned in the posterior pharnyx. Air was withdrawn at this position and sampled by a rapidly responding O_3 analyzer,resulting in real time measurements of inhaled and exhaled O_3 concentrations. This arrangement allowed for the determination of the absorption efficiencies both proximal and distal to the posterior pharynx. The efficiencies were determined as a function of O_3 concentration (0.1, 0.2 and 0.4 ppm), respiratory frequency (12 and 24 bpm), and breathing mode (mouth only,

nose only and oronasal). The mean O_3 removal efficiency proximal to the posterior pharynx was 39.6 $\pm$ 0.7 (SEM) percent. Significantly less O_3 was removed at 24 bpm than at 12 bpm (38.2 and 41.0 percent respectively), O_3 concentration had no effect on removal from the upper region, and significantly less O_3 was removed during nasal breathing than during the other two modes (36.0, 40.0, and 42.8 percent for nasal, mouth and oronasal,respectively).

Lower Respiratory Tract Uptake Experiments

Formaldehyde

HCHO uptake in the lower respiratory tract of dogs was measured by Egle (1972). Ninety five to one hundred percent of the inspired HCHO was retained, the data suggesting that the percent uptake decreased with increased ventilatory rate.

Ozone

Yokoyama and Frank (1972) measured the removal of O_3 from inspired air in the ventilated lower respiratory tract of beagle dogs. The uptake was found to vary between 80 and 87%, independent of the two levels of concentration (.77 ppm and 0.3 ppm) and the two flow rates (20 or 30 breaths/min).

Gerrity et al.(1987) measured the absorption efficiencies of the region of the RT distal to the posterior pharynx. A brief description of the experimental arrangement is given in the previous section. The mean absorption efficiency was 91.0 $\pm$ 0.5 percent of the O_3 inhaled through the posterior pharynx. Significantly more O_3 was absorbed at 12 bpm than at 24 bpm (92.6% compared to 89.3%), and significantly less O_3 was removed at 0.1 ppm than at 0.4 ppm (89.4, 90.9 and 92.5

percent for 0.1, 0.2 and 0.4 ppm, respectively). No differences in uptake due to mode of breathing were detected.

Nitrogen Dioxide

Corn et al., (1976) determined the average mass transfer coefficient (K) of NO_2 in the LRT of cats. The region of measurement was between the trachea and a portion of the lung associated with the "right lateral thoracic region between the fourth and fifth rib" (Corn et al., 1976). They reported no change in K as a result of NO_2 concentration changes or ventilatory rate changes. However, NRC (1977) claims the data on K (from Corn et al., 1976) show a square root dependency on frequency. Postlethwait and Mustafa (1981) reported the uptake of NO_2 by an isolated perfused rat lung. The isolated lungs were exposed for 90 minutes to 5 ppm NO_2 at a ventilation rate of 45 ml/min. Thirty six percent of the ventilated NO_2 was absorbed.

Total Uptake Experiments

Formaldehyde

Experiments were carried out by Egle (1972) to determine the total uptake of HCHO in dogs. Retention varried from 95% - 100% regardless of the tidal volume (100 ml to 200 ml) or ventilatory rate (8 - 20 breath/min). However, a slight increase in percent uptake was observed with increasing HCHO concentration.

Ozone

Wiester et al. (1987) determined the uptake of O_3 in awake adult rats in a head out plethysmograph. The rats breathed for one hour, either 0.3, 0.6 or 1.0 ppm O_3. Of the O_3 inhaled, 40 $\pm$ 11 (standard deviation) percent was retained, independent of time and concentration. Further, the total dose was proportional to concentration.

Nitrogen Dioxide

Adult asthmatics were exposed to 0.3 ppm NO_2 for 30 minutes by Bauer et al., (1984). All exposed subjects inhaled NO_2 by mouthpiece for 20 minutes at rest, then exercised for 10 minutes on a bicycle ergometer. The inspired and expired NO_2 concentrations were measured showing that at rest the uptake was 73 +/- 6% (SD); whereas, during exercise the uptake was 88 +/- 4 %, a significant increase. Minute ventilations during the rest and exercise periods were 8.1 L/min and 30.4 L/min, respectively; for the same period of time, 4.8 times as much NO_2 was absorbed during exercise as during rest (Morrow, 1986).

PREDICTIONS OF LRT ABSORPTION OF O_3 IN ANIMALS AND HUMANS

The effect of anatomical models on the distribution of predicted absorbed O_3 in the LRT

The effects of different anatomical models on the distribution and uptake of absorbed O_3 in the LRT of rats and guinea pigs were investigated by Overton et al. (1987a). Two anatomical models were used for each species. Figure 3 shows the simulated tissue and net dose profiles for the four anatomical models. The doses are plotted versus generation, order or zone, depending on the particular anatomical model as defined by the original investigators for each model.

The plots are typical, the general shapes being independent of ventilatory parameters, and illustrate some of the similarities and differences in predictions using the different anatomical models. Generally, the tissue dose is low in the trachea, rising to a maximum value in the vicinity of the centriacinar region. From here, and

proceeding distally in the pulmonary region, the tissue dose rapidly decreases. Net dose is large in the trachea, decreasing distally to the pulmonary region where the net dose either rapidly increases or continues to decrease, depending on the anatomical model. Tissue and net dose are approximately the same in the pulmonary region.

The plots resulting from using the Kliment (1973) anatomical models of the guinea pig and rat (Figures 3A and 3C) are similiar in shape, except at the 6th and 7th zones where the guinea pig tissue dose peaks in contrast to the rat tissue dose curve that plateaus and then decreases. This difference reflects the choice of where the surfactant lined or pulmonary region begins. For the guinea pig, the region begins at the 6th zone and for the rat the region begins in the 7th zone. Pulmonary and total uptake for the Kliment rat (Figure 3c) are 81 and 87 percent, respectively. For the Kliment (1973) guinea pig, the uptakes are 85 and 92 percent, respectively.

The similarity of rat and guinea pig dose profiles, as predicted by use of the Kliment (1973) anatomical models, does not extend to the predictions made by use of the Schreider and Hutchens (1980) and the Yeh et al. (1979) anatomical models for the guinea pig (Figure 3B) and rat (Figure 3D). These two models result in considerable differences. For example, the net tracheal dose for the rat is smaller than the tissue and net dose of the first alveolated duct. On the other hand, the net dose predicted for the trachea of the guinea pig is approximately 7 times larger than the net dose predicted for the first completely alveolated duct of this species. However, the net dose profiles are alike in that they peak in the first alveolated generation or order, a feature not present in the simulations using the anatomical models of Kliment (1973).

The intra- and interspecies differences in predicted dose profiles (Figures 3) may be more a result of incorrect or unrepresentative anatomical model characterizations than due to actual differences between or within species. Nevertheless, the results show the importance of anatomical dimensions on predicted absorption in the LRT and the need for correctly specified anatomical models. For a further discussion of this aspect see Overton et al. (1987a).

The Effect of TB Liquid Lining Thickness on Predictions

Miller et al. (1985) showed that the thickness of the liquid lining of the TB region and the respiratory bronchioles (RB) is critical to the prediction of tissue dose in the TB region. Figure 4 shows the effects of three TB/RB liquid lining thickness schemes on tissue dose using the anatomical model of Weibel (1963) for man. The reference thickness (resulting in curves A and A') are 10.0, 8.6, and 7.2 μm in generations 0, 1, and 2, respectively. From generation 2 through generation 20, thickness is assumed to decrease linearly with respect to generation index. Generation 20 is the first completely alveolated generation in the Weibel (1963) anatomical model. From generation 20 to 23, the liquid lining thickness is assuned to be 0.125 μm. The thickness schemes for curves B/B' and C/C' are such that for generations 0 to 19 the B/B' thicknesses are one half those of the reference values, and the C/C' thicknesses are twice those of the reference values. Values of the thicknesses of the three schemes are within the range of reported values (see Table 2 -- note that some of the investigators reported thickness above the hypophase and others reported the total liquid lining thickness).

The most obvious effect of thickness change is the pronounced decrease in TB tissue dose (curves A, B, C) as the thickness increases; whereas, the net doses (curves A', B', C') are hardly affected. In general, tracheal tissue dose is very low and is different for the three thicknesses, with more than two orders of magnitude separating the extreme values of tracheal tissue doses. From the trachea, the tissue doses increase distally to a maximum near the terminal bronchioles (generation 16). For the thinest lining (curve B), the maximum occurs in the 15th generation. Two maximums occur for the reference thickness lining (curve A), one at the 15th and the other at the 17th generation (first respiratory bronchioles). The tissue dose for the thickest lining occurs in the first order of respiratory bronchioles. In all three cases, the tissue dose decreases distally from the last maximum to very low values in the pulmonary sacs (generation 23).

The net doses (Figure 4, curves A', B',C') for the three thicknesses are the same in the trachea. Proceeding distally, the net dose curves split, the largest (curve B') and smallest (curve C') net doses corresponding to the thinnest and thickest lining, respectively. At the 16th generation they differ by a factor of about 1.5; from the first respiratory bronchiles (generation 17) to the pulmonary sacs, they differ by no more than a factor of two.

Interspecies Comparison of LRT Dose Patterns

In Figures 5A and B are plotted the LRT net and tissue dose curves for four species - rabbit, guinea pig, rat, and man. Depending on the particular anatomical model, the plots are dose versus zone (Kliment, 1973, rabbit),

order (Schreider and Hutchens, 1980, guinea pig), and generation (Yeh et al., 1979, rat; Weibel, 1963, man). Because of the construction of the anatomical models, it is not possible to have a one-to-one correspondence between the horizontal axis of a zone, order, or generation, thus the four axes. However, we have matched those segments (the sequential groupings of airways, duct and sacs as defined for the particular model) that are equivalent. These include the tracheas, the last TB segments, the first RB in man and the first completely alveolated segments in the non-human species, and the last pulmonary segments.

The general shapes of the net dose curves (Figure 5A) are the same, slowly decreasing distally in the TB region, with a more rapid decrease distally in the pulmonary region. There are differences in detail: the rat net dose peaks in the first segment of the pulmonary region, and the guinea pig net dose has a local maximun at this location. The net doses of both the human and rabbit continuously decrease with no peak.

Tissue dose (Figure 5B) is low in the trachea for all four species, being almost three orders of magnitude less than the tracheal net doses. Proceedingly distally, the tissue doses increase to a maximum in the vicinity of the first segment in the pulmonary region, and then decrease rapidly. The rabbit maximum occurs in the last segment of the TB region; whereas, the maximum guinea pig, rat, and human tissue doses occur in the first segment of the pulmonary region, a location where histopathological data show the major lesions in O_3 studies using monkeys (see, e.g., Dungworth et al., 1975) and rats (e.g., Boorman et al., 1980).

The results shown in Figures 5A and 5B were obtained with an appropriate URT model "attached" to each LRT anatomical model in order to take into account the effect of URT volume; however, no URT absorption was simulated. Accounting for URT absorption in each species would lower the predicted doses by an amount depending on each species' URT absorption, and also, possibly, put the curves in a vertical order different than plotted in Figures 5A and 5B. To make more definitive interspecies quantitative comparisons, URT removal must be considered.

The Effect of the TB Region Liquid Lining Chemical Rate Constant on O_3 Uptake

The effect on regional and compartmental dose in rats and man due to different values of the TB liquid lining rate constant was investigated (Table 9). For the investigation, the anatomical models of Weibel (1963) for man and Yeh et al. (1979) for rats were used. Three values of the rate constant were chosen, one-fifth the reference value, the reference value, and five times the reference value (i.e., the value based on reference material data. See Miller et al., 1985 and Overton et al., 1987a). Refering to Table 9, one can see that by increasing the rate constant of both species, the total uptakes, the total TB region uptakes, and the TB liquid lining uptakes increase, whereas the TB tissue uptakes and the pulmonary region uptakes decrease. The largest changes occur in the TB region where the total rat TB tissue dose nearly triples and the TB tissue dose in man increases by a factor of 2.5. On the other hand, the total LRT uptakes change by only a few percent, increasing 8 and 4.4 % for the rat and man, respectively.

The change in pulmonary tissue dose is larger, being - 19 and - 31 % for rats and humans, respectively.

The quantitative aspects of the changes illustrated in Table 9 in the percent uptakes will depend on other factors in addition to the rate constant, including V_T and f. However, the qualitative aspects of the changes may be independent of these other parameter values. For example, for the rat, Overton et al. (1987a) showed that for two values of the functional residual capacity and two sets of different ventilatory parameters, the qualitative aspects of uptake changes due to increasing the rate constant remained the same.

SUMMARY

In inhalation toxicology an important concept involves the determination of dose as a major component for providing a perspective to judge the applicability of various toxicological results to human exposure conditions. This chapter reviewed some of the biological, physical, and chemical factors that affect dose and that must be understood to interpret experimental toxicological data and to develop theoretical dosimetry models. Dosimetry experiments involving laboratory animals and humans were briefly discussed, showing the variability in uptake according to the reactive gas, animal species, and respiratory tract region. The results of theoretical dosimetry models were illustrated showing the effects on predictions due to different inter- and intraspecies LRT anatomical models, due to different TB liquid lining thicknesses, and due to the chemical rate constant of the liquid lining of the TB region. Also illustrated was the use of predictions for interspecies dosimetry comparisons by comparing the dose profiles of rat, guinea pig, rabbit and human. In spite of the complexities

involved in experimental or theoretical dosimetry, results so far illustrate the feasibility of making interspecies LRT dosimetry comparisons for evaluating the toxicity of inhaled toxic gases, of providing sensitivity studies to determine processes and parameters needing additional research, and of assisting in experimental design.

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TABLE 1*

Schematic Representation of Respiratory Tract of Guinea Pig

Region	Diameter of Duct or Alveolus (cm)	Length (cm) of Duct	Vol. of Duct or Alveolus (cm^3)	No. of Ducts or Alveoli	Alveoli/ Duct	Alveoli/ Region
Nasal cavity			0.48	1		
Nasopharynx	0.32	2.5	0.20	1		
Trachea	0.30	4.5	0.32	1		
1st order bronchi	0.22	1.2	0.042	2		
2nd order bronchi	0.16	1.9	0.037	5		
3rd order bronchi	0.10	0.85	6.6×10^{-3}	17		
4th order bronchi	0.065	0.53	1.8×10^{-3}	86		
5th order bronchi	0.050	0.26	5.1×10^{-4}	312		
6th order bronchi	0.040	0.19	1.9×10^{-4}	1.0×10^{3}		
7th order bronchi	0.030	0.10	7.1×10^{-5}	3.0×10^{3}		
8th order bronchi	0.023	0.066	2.6×10^{-5}	9.5×10^{3}		
9th order bronchi	0.014	0.045	7.0×10^{-6}	4.2×10^{4}		
1st alveolated duct	0.009	0.024	1.6×10^{-6}	1.3×10^{5}	23	2.88×10^{6}
2nd alveolated duct	0.007	0.024	9.2×10^{-7}	2.5×10^{5}	21	5.41×10^{6}
3rd alveolated duct	0.006	0.024	6.8×10^{-7}	5.0×10^{5}	19	9.46×10^{6}
4th alveolated duct	0.006	0.024	6.8×10^{-7}	1.0×10^{6}	19	1.89×10^{7}
5th alveolated duct	0.005	0.032	6.3×10^{-7}	2.0×10^{6}	23	4.55×10^{7}
Alveoli	0.008		2.0×10^{-7}	8.2×10^{7}		

*Based on Tables 2 and 3, Schreider and Hutchens (1980).

TABLE 2

Tracheobronchial and URT Liquid Lining Thicknesses

Species	Location	Thickness[a] (μ)	Comments	Investigators
rats	nose	≤15	Observed a continuous blanket.	Morgan et al. (1984)
monkey	nose	not given	Observed two layers, an "overlying viscid sheet and a layer of serous fluid."	Lucas and Douglas(1934)
cats	trachea	≤20; usually <10	Not uniform; "in some areas not detected."	Adler (1973)
rats	trachea, large bronchi	5-10	"distribution was focal"	Yoneda (1976)
guinea pigs	trachea	~10	"constantly biphasic"	Hulbert et al. (1982)
	intra-pulmonary	0.0	Liquid lining never extended beyond ciliary tips.	
rats	terminal bronchiole	0.0	(no epiphase or mucus observed in healthy rats).	Stevens et al. (1974); Iravani and van As (1972)
rabbit	bronchi (1-3 mm)[b]	5 or more[c]	Mucous blanket observed	Luchtel (1976)
	bronchioles (0.5-1.0 mm)[b]	1-4[c]		
	bronchioles (< .5 mm)[b]	0.3-0.5[c]		
	terminal bronchioles	<0.1[c]		
rat	trachea	3-15;[c] generally 8-12[c]	Mucous blanket observed	Luchtel (1978)
	lobar bronchi	few tenths-8;[c] generally 2-5[c]		

TABLE 2 (Continued)

Measurements of Tracheobronchial and URT Liquid Lining Thicknesses

Species	Location	Thickness (μ)	Comments	Investigators
rats	trachea, major bronchi, peripheral airways	- -	"well defined streams up to 500 m wide." "Mucus was transported as discrete particles" as small as 0.5m in diameter. A continuous mucous blanket was not observed.	Iravani van As (1972) van As and Webster (1972, 1974)

[a]Unless otherwise specified "thickness" applies only to the epiphase above cilia tips.

[b]Diameter range of airways.

[c]Total liquid lining thickness (epiphase plus hypophase).

TABLE 3*

Alveolar Region Tissue and Blood Compartments Dimensions of Normal Mammalian Lungs

	Fischer 344 Rat (n = 4)	Sprague-Dawley Rat (n = 8)	Dog (n = 4)	Baboon (n = 5)	Human (n = 8)
Body weight, kg	0.29 ± 0.01	0.36 ± 0.01	16 ± 3	29 ± 3	79 ± 4
Lung volume, ml	8.6 ± 0.31	10.55 ± 0.37	1322 ± 64	2393 ± 100	4341 ± 284
Total volumes, cm^3/both lungs					
Air	5.978 ± 0.197	7.216 ± 0.278	914 ± 52	1851 ± 24	3422 ± 223
Capillary lumen	0.649 ± 0.057	0.659 ± 0.055	92 ± 5	44 ± 17	169 ± 24
Tissue	0.428 ± 0.046	0.671 ± 0.041	78 ± 4	68 ± 9	314 ± 41
Type I epithelium	0.082 ± 0.006	0.144 ± 0.010	16.5 ± 1.9	14.4 ± 2.3	32.5 ± 3.9
Type II epithelium	0.037 ± 0.009	0.053 ± 0.009	5.6 ± 0.5	3.5 ± 0.8	32.1 ± 5.0
Cellular interstitium	0.068 ± 0.005	0.079 ± 0.015	12.9 ± 0.7	9.4 ± 1.6	54.0 ± 7.0
Noncellular interstitium	0.128 ± 0.016	0.214 ± 0.016	22.8 ± 0.7	24.6 ± 3.7	98.3 ± 12.4
Endothelium	0.094 ± 0.009	0.156 ± 0.007	17.6 ± 1.6	13.4 ± 2.6	42.6 ± 5.4
Macrophages	0.019 ± 0.007	0.025 ± 0.006	2.5 ± 1.1	2.4 ± 1.1	54.7 ± 15.7
Surface area, m^2/both lungs					
Alveolar epithelium					
Type I	0.391 ± 0.039	0.387 ± 0.025	51.0 ± 1.0	47.7 ± 7.7	89.0 ± 8.0
Type II	0.015 ± 0.005	0.015 ± 0.002	1.0 ± 0.2	1.9 ± 0.3	7.0 ± 1.0
Capillary endothelium	0.383 ± 0.039	0.452 ± 0.035	57.0 ± 2.0	38.6 ± 9.5	91.0 ± 9.0
Tissue component of diffusion capacity, ml $O_2 \cdot min^{-1} \cdot mm\ Hg^{-1}$	3.43 ± 0.17	3.55 ± 0.33	399 ± 12	231 ± 52	436 ± 53.6
Tissue thickness, μm					
Harmonic mean, air-to-plasma	0.379 ± 0.030	0.405 ± 0.017	0.450 ± 0.007	0.674 ± 0.055	0.745 ± 0.059
Arithmetic mean					
Epithelium					
Type I	0.212 ± 0.008	0.384 ± 0.038	0.327 ± 0.043	0.308 ± 0.021	0.361 ± 0.024
Type II	2.758 ± 0.424	3.653 ± 0.266	4.138 ± 0.340	1.839 ± 0.141	5.019 ± 0.551
Interstitium	0.500 ± 0.028	0.693 ± 0.058	0.658 ± 0.033	0.847 ± 0.140	1.634 ± 0.164
Endothelium	0.246 ± 0.011	0.358 ± 0.031	0.308 ± 0.019	0.361 ± 0.038	0.474 ± 0.052

*Based on Table 1, Crapo et al. (1983); all data are mean ± SE.

TABLE 4

Unsaturated Fatty Acid Composition and Concentration[a] of Human Lung Secretions, Tissue, and Blood

Fatty Acid	Mucus[b]	Surfactant[c]	Lung Tissue[d]	Whole Blood[e]
16:1	0.0738	0.004	8.08	0.12
18:1	0.657	0.0087	25.0	0.77
18:2	0.20	0.0018	8.2	1.12
18:3	0.0006	0.001	-	0.036
20:1	-	-	-	0.006
20:2	0.035	-	-	-
20:3	-	-	-	0.034
20:4	-	0.0005	-	0.23
10:5	-	-	-	0.06
22:5	-	-	-	0.02
22:6	-	-	-	0.07

[a]μmole per gm wet weight. Omitted values (-) correspond to no or insufficient data.

[b]Data derived using Lewis (1971).

[c]Data derived using Sahu and Lynn (1977).

[d]Data derived using Clements (1971), Altman and Dittmer (1974), and Sanders (1982).

[e]Data derived using Nelson (1972), Gier et al. (1964), Phillips and Dodge (1967), and Hallgren et al. (1960).

TABLE 5

Amino Acid Concentration[a] and Composition of Human Lung Tissue, Secretions and Blood

Amino Acid	Lung[b] Tissue	Mucus[c]	Surfactant[d]	Whole Blood[e]
Cysteine	33	0.8	0.007	19.4
Methionine	23	0.6	0.006	17.0
Tryptophan	17	0.3	<0.001	15.6
Tyrosine	45	1.1	0.016	33.6
Histidine	30	0.7	0.009	78.3
Phenylalanine	51	0.8	0.018	70.8
Total	199	4.3	0.056	234.7

[a]Data are in units of μmoles/gm wet weight.

[b]Data derived using Altman and Dittmer (1974); Farrell (1982); Blackburn et al. (1983).

[c]Data derived using Boat and Cheng (1980); Riley and Brogan (1973); Creeth et al. (1977); Khler et al. (1969).

[d]Only the monomolecular surface active film. Data derived using Sahu and Lynn (1977); Passero et al. (1973); Sahu and Lynn (1979).

[e]Data derived using Blackburan et al. (1983); Lehninger (1975); Fasman (1976).

TABLE 6

Chemical Reaction Mechanism of the CO_2 - O_3 - SO_2 and Nitrogen Oxide Aqueous System[1]

1.	$H_2O \rightleftharpoons H^+ + OH^-$	10.	$HNO_2 + HNO_2 \rightleftharpoons N_2O_3 + H_2O$
2.	$CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$	11.	$N_2O_3 \rightleftharpoons NO + NO_2$
3.	$HCO_3^- \rightleftharpoons OH^- + CO_2$	12.	$NH_3 + H^+ \rightleftharpoons NH_4^+$
4.	$SO_2 + H_2O \rightleftharpoons H^+ + HSO_3^-$	13.	$NH_3 \rightleftharpoons NH_4^+ + OH^-$
5.	$HSO_3^- \rightleftharpoons H^+ + SO_3^{2-}$	14.	$O_3 + SO_2 \rightleftharpoons SO_4^{2-} + 2H^+$
6.	$NO_2 + NO_2 \rightleftharpoons N_2O_4$	15.	$O_3 + SO_3^{2-} \rightleftharpoons SO_4^{2-}$
7.	$N_2O_4 + H_2O \rightleftharpoons HNO_2 + HNO_3$	16.	$O_3 + HSO_3^- \rightleftharpoons H^+ + SO_4^{2-}$
8.	$HNO_2 \rightleftharpoons H^+ + NO_2^-$	17.	$O_3 + NO_2^- \rightleftharpoons NO_3^-$
9.	$HNO_3 \rightleftharpoons H^+ + NO_3^-$		

[1]Based on Durham et al. (1984, 1981)

TABLE 7

Henry's Law Constant for Selected Gases in Water

Gas	Henry's Law Constant[a]	Source	Major Site of Toxicity or Absorption[b]
Nitrogen (N_2)	77.	Altman and Dittmer (1971)	P
Carbon Monoxide (CO)	55.	Altman and Dittmer (1971)	P
Oxygen (O_2)	42.	Altman and Dittmer (1971)	P
Nitrogen Oxide (NO)	24.	Perry and Chilton (1973)	TB and P
Ethylene (C_2H_4)	13.	Altman and Dittmer (1971)	
Nitrogen Dioxide (NO_2)	8.8[c]	Lee and Schwartz (1981)	TB and P
Ozone (O_3)	6.4	Roth and Sullivan (1981)	TB and P
Methane (CH_4)	3.5	Perry and Chilton (1973)	
Carbonyl Sulfide (COS)	2.8	Perry and Chilton (1973)	
Nitrous Oxide (N_2O)	2.4	Perry and Chilton (1973)	
Carbon dioxide (CO_2)	1.8	Altman and Dittmer (1971)	P
Acetylene (C_2H_2)	1.3	Altman and Dittmer (1971)	
Formaldehyde (HCHO)	.56	NRC (1977)	URT
Hydrogen Sulfide (H_2S)	0.5	Perry and Chilton (1973)	URT and large bronchi
Sulfur Dioxide (SO_2)	0.048	Hales and Sutter (1973)	
Ammonia (NH_3)	0.0011	Perry and Chilton (1973)	URT

[a] 37°C; (moles/liter/air)/(moles/liter/water)

[b] NRC (1977). TB = tracheobronchial region; URT = upper respiratory tract; P = pulmonary region.

[c] Extrapolation to 37° based on the temperature dependence of ozone.

TABLE 8

Henry's Law Constant for Various Gases in Fluids and Tissue*

	LIQUIDS						TISSUE				
	Water	Water (.155N NaCl)	Whole Blood		Plasma		Heart		Brain		Lung (rat)
			man	dog	man	dog	man	dog	man	dog	
O_2	42	45	43	-	48	-	-	-	-	-	56
CO_2	1.8	1.9	2.0	-	1.9	-	-	-	-	-	-
C_2H_4	13	-	8.1	7.1	-	-	-	-	-	-	-
C_2H_2	1.3	-	1.4	1.3	-	1.4	-	-	-	-	-
N_2O	-	-	2.4	2.4	-	-	2.2	2.2	2.3	2.3	-
N_2	77	83	-	-	-	-	-	-	-	-	-

*Altman and Dittmer, 1971. Values are in units of (moles/liter in air) per (moles/liter in solvent).

TABLE 9

Effect of TB Liquid Lining Rate Constant on the Uptake of O_3 in the Regions and Compartments of the LRT of Rat and Man[a]

	($k_\mu/k_{\mu ref}$)[b]	Total LRT Uptake %	Tracheobronchial Region Uptake (%)			Pulmonary Region Uptake (%c)	
			Liquid Lining	Tissue	Total TB	Tissue	Blood
Rat[d]	0.2	70.5	2.9	5.6	8.5	60.7	1.2
V_T = 2.40 ml	1.0	72.4	9.2	3.9	13.1	58.1	1.2
f = 81 bpm	5.0	76.4	22.6	1.6	24.2	51.1	1.0
Human	0.2	88.6	4.8	12.4	17.2	69.3	2.0
V_T = 800. ml	1.0	90.1	17.2	8.0	25.2	63.0	1.8
f = 15 bpm	5.0	92.5	41.3	1.9	43.2	47.8	1.4

[a]Uptake is the percentage of O_3 inhaled through the trachea that was absorbed by the region and compartment.

[b]k_μ = TB liquid lining rate constant; $k_{\mu ref}$ = reference TB liquid lining rate constant.

[c]Pulmonary liquid lining absorbes <0.1%.

[d]Rat data from Table 3, Overton et al. (1987a).

Figure Legends

1. The relationships between morphologies and their model representations. Panel a is a schematic of the branching airways of the TB and pulmonary region of man. The generations are labeled from the right, beginning with the trachea. BR, BL and TBL indicate bronchi, bronchioles and terminal bronchioles, respectively; the respiratory bronchioles, alveolar ducts, and alveolar sacs are indicated by RBL, AD and AS, respectively. Below the TB portion of the lung schematic are three cylindrical figures that indicate the model representation of the airways. Panel c shows a diagram of the structure of the liquid lining and tissue of the TB region. The different cells represented are basal (BC), ciliated (CC), brush (BrC), goblet (GC), and nonciliated serous (NCC). Panel e illustrates the model representation of TB liquid lining and tissue compartments. On the left side of the figure, Panel b, is an electron micrograph of the interalveolar septa. The air spaces (A), capillaries (C), type I cells and their nuclei (EP1 and NEP1), endothelial cells and their nuclei (EN and NEN), and interstitial space (IN) are indicated. Panel d illustrates the model representation of the liquid lining, tissue and capillaries of the pulmonary region. (Figure reprinted from Miller et al. 1987a.)

2. A stylized diagram illustrating the type of respiratory tract anatomical models used with the dosimetry model.

3. An illustration of the effect of four different lower respiratory tract anatomical models on predicted net and tissue O_3 dose profiles of guinea pig and rat. Dose is the quantity of O_3 reacting with biological constituents per unit surface area of a zone, order or generation, per unit time per tracheal O_3 concentration. Net dose is the sum of the

liquid lining, tissue and blood compartment doses.

A. Dose versus zone, Kliment (1973) anatomical model for guinea pig, V_T = 2.53 ml, f = 56.6 BPM.

B. Dose versus order, Schreider and Hutchens (1980) anatomical model for guinea pig, V_T = 2.4 ml, f = 77 BPM.

C. Dose versus zone, Kliment (1973) anatomical model for rat, V_T = 0.7 ml, f = 144 BPM.

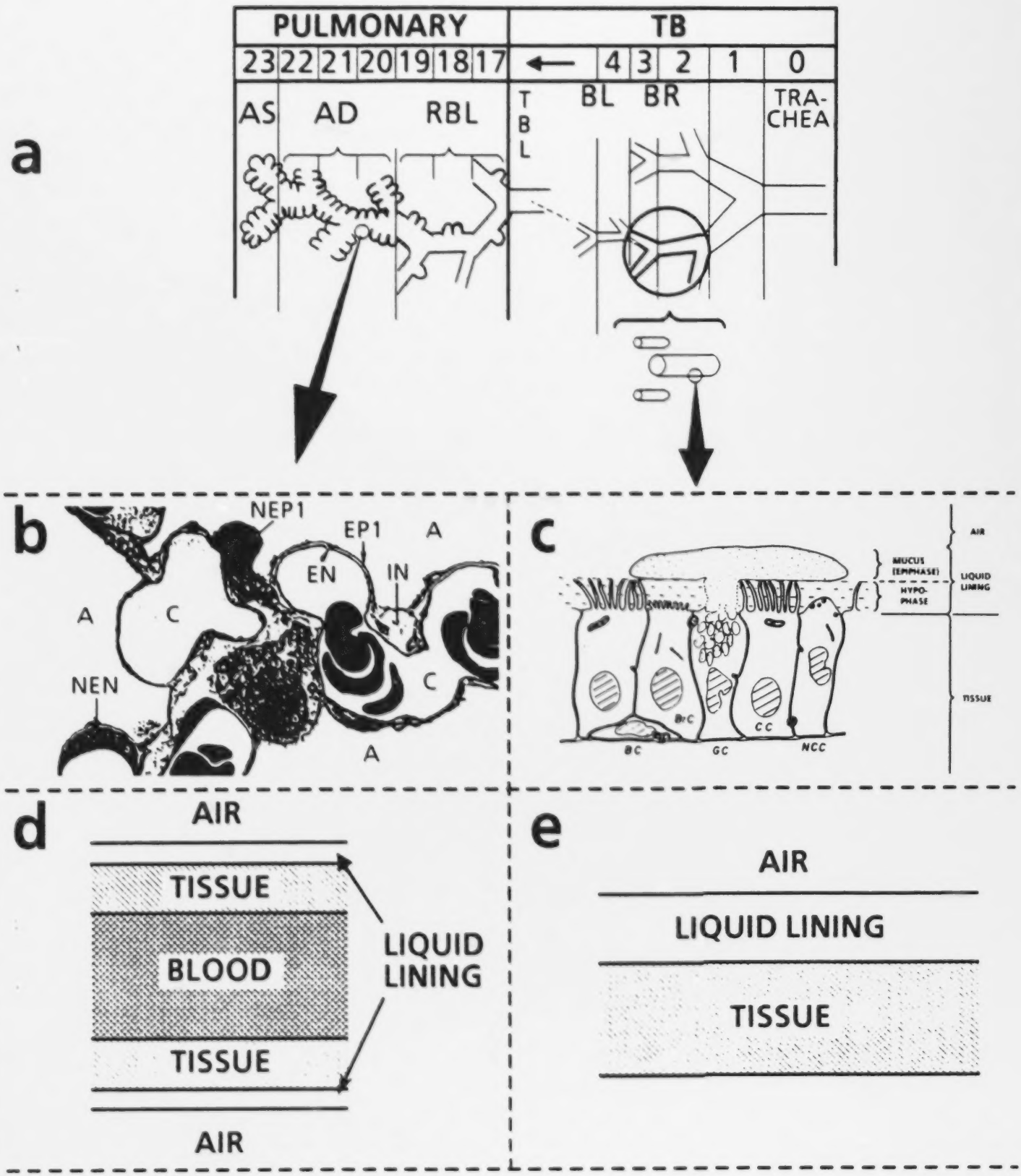
D. Dose versus generation, Yeh et al. (1979) anatomical model for the rat, V_T = 1.84 ml, f = 105 BPM.

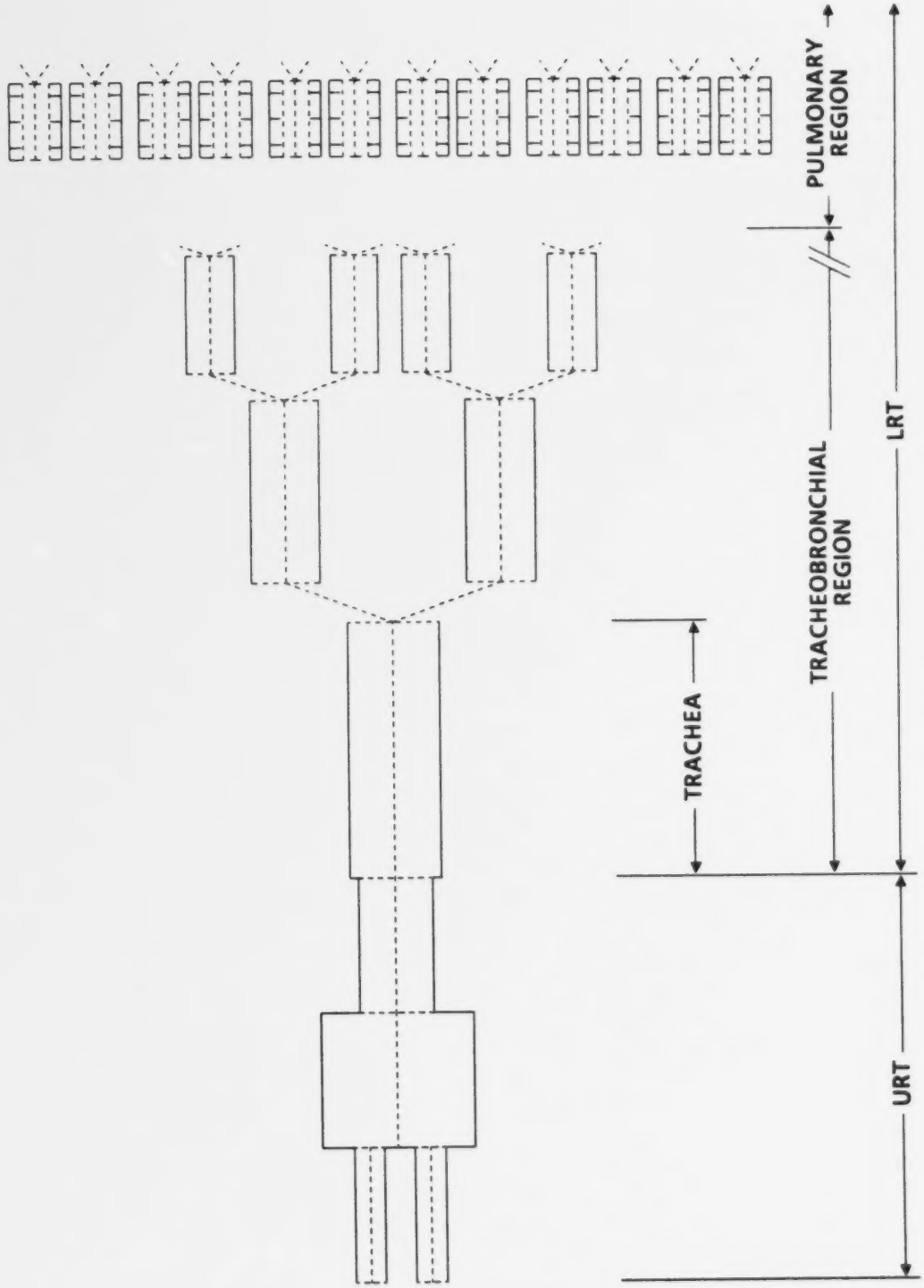
TB = Tracheobronchial region (mucus lined); P = pulmonary region (surfactant lined). Multiply figure values by tracheal concentration ($\mu g/m^3$) to obtain dose ($\mu g/cm^2$ per minute). (Figure from Overton et al., 1987a.)

4. The effect of liquid compartment thickness schemes on O_3 tissue dose (curves A, B and C) and on the corresponding net dose (A', B' and C'). Curves A and A': reference curves, thickness scheme A. Curves B and B': thickness scheme B (one-half thickness of scheme A). Curves C and C': thickness scheme C (twice thickness of scheme A). TB = tracheobronchial region (mucous lined); P = pulmonary region (surfactant lined). Multiply figure values by tracheal concentration ($\mu g/m^3$) to obtain dose ($\mu g/cm^2$ per breath). (From Miller et al., 1985.)

5. Net dose (5A) and tissue dose (5B) versus sequential segments along anatomical model airway paths for man, rat, guinea pig and rabbit. In general, each segment represents a group of airways or ducts with common features as defined by the designers of the anatomical model (man and rat: generation; guinea pig: order; rabbit: zone). For a given species the

plotted "dots" represent a predicted dose that corresponds to a given segment. The dots have been joined by lines for ease of interpreting the plots; these lines do not represent predicted values except where they intercept the dots. (From Miller et al., 1987b.)


a
PULMONARY
TB
23 22 21 20 19 18 17
4 3 2 1 0
AS
AD
RBL
TBL
BL
BR
TRA-CHEA
b
NEP1
EP1
A
EN
IN
A
C
NEN
C
A
c
AIR
MUCUS (EMPHASE)
HYPO-PHASE
LIQUID LINING
TISSUE
BC
GC
NCC
d
AIR
TISSUE
BLOOD
TISSUE
AIR
LIQUID LINING
e
AIR
LIQUID LINING
TISSUE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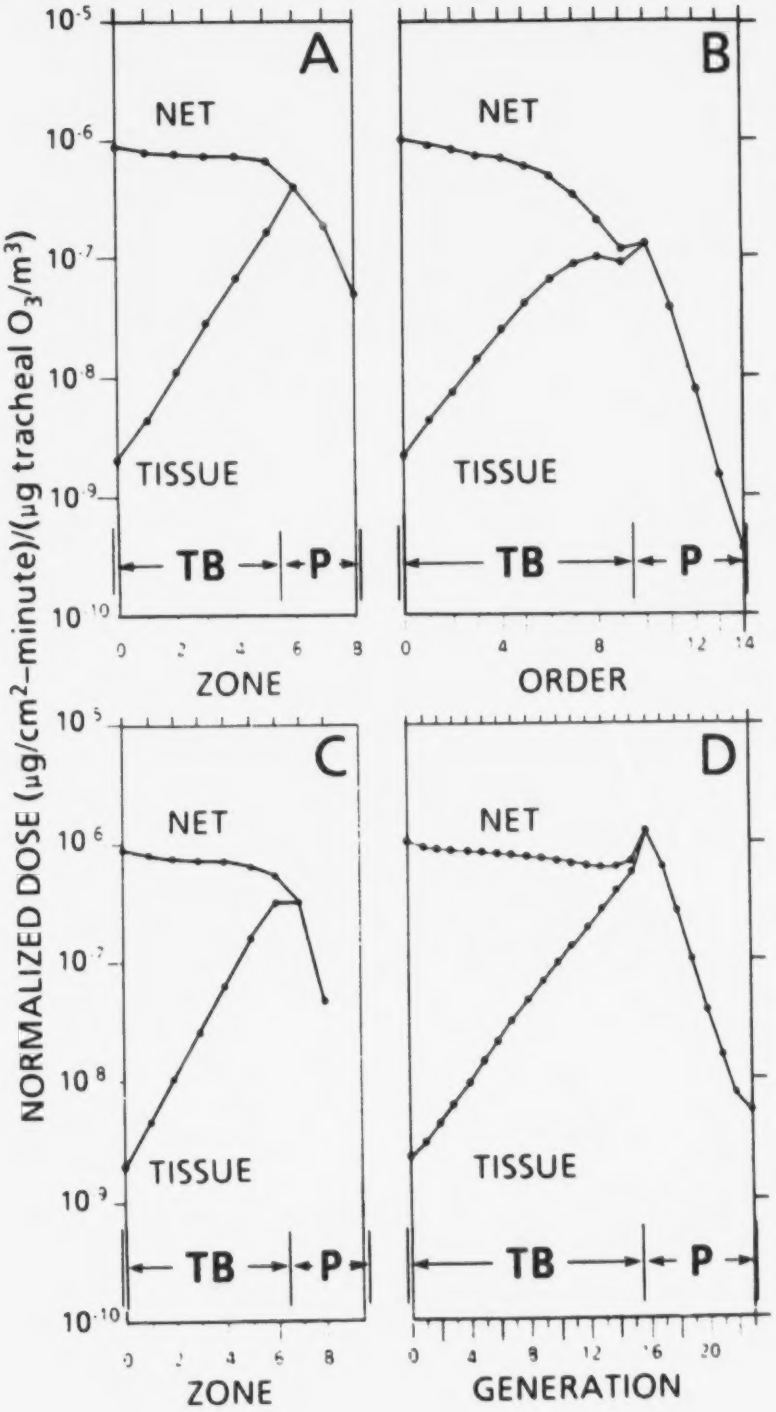
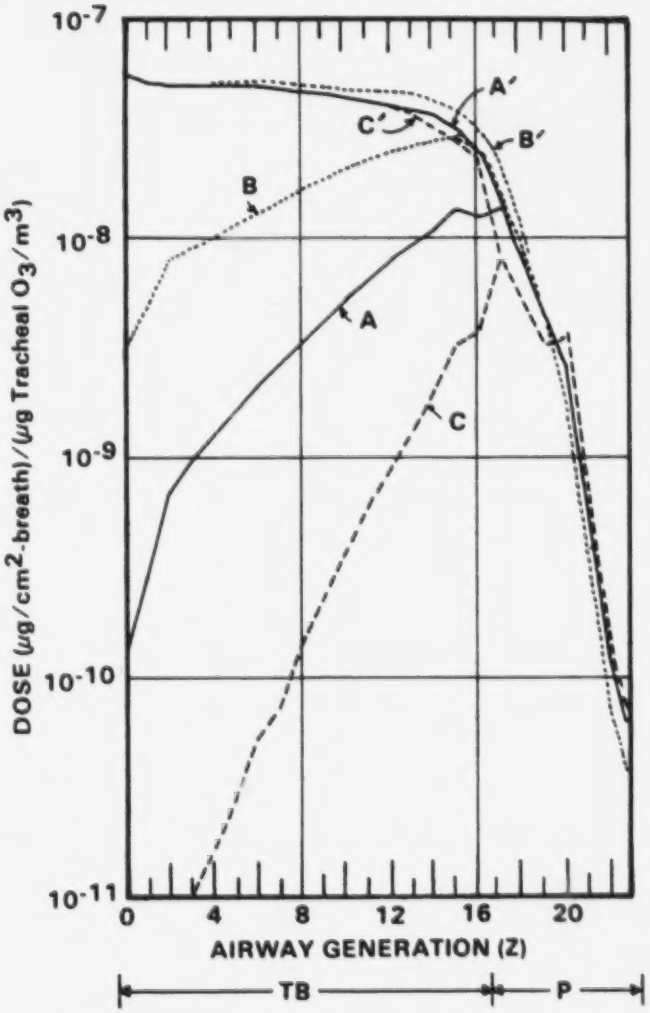
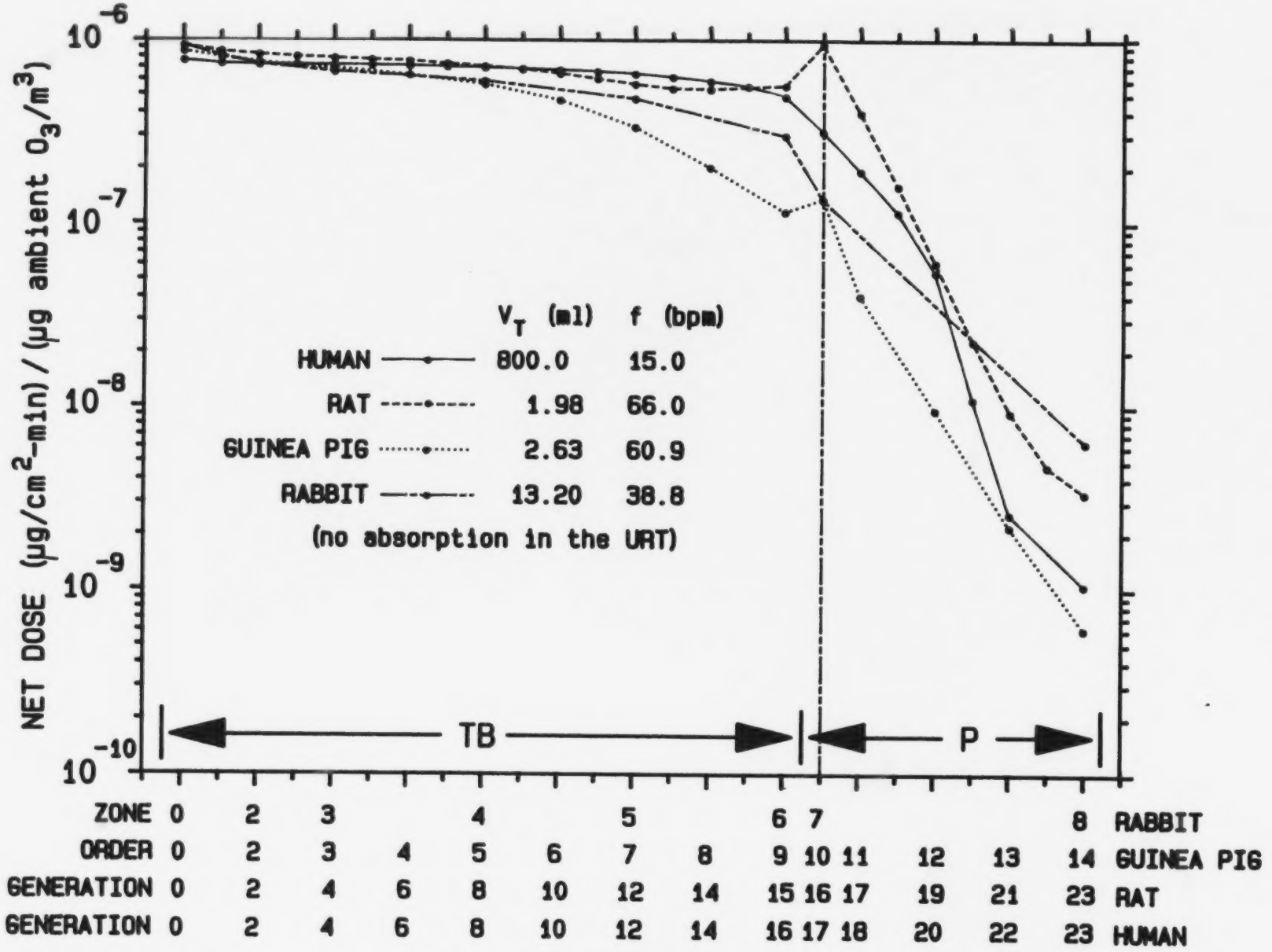
TRACHEOBRONCHIAL REGION
TRACHEA
LRT
URT

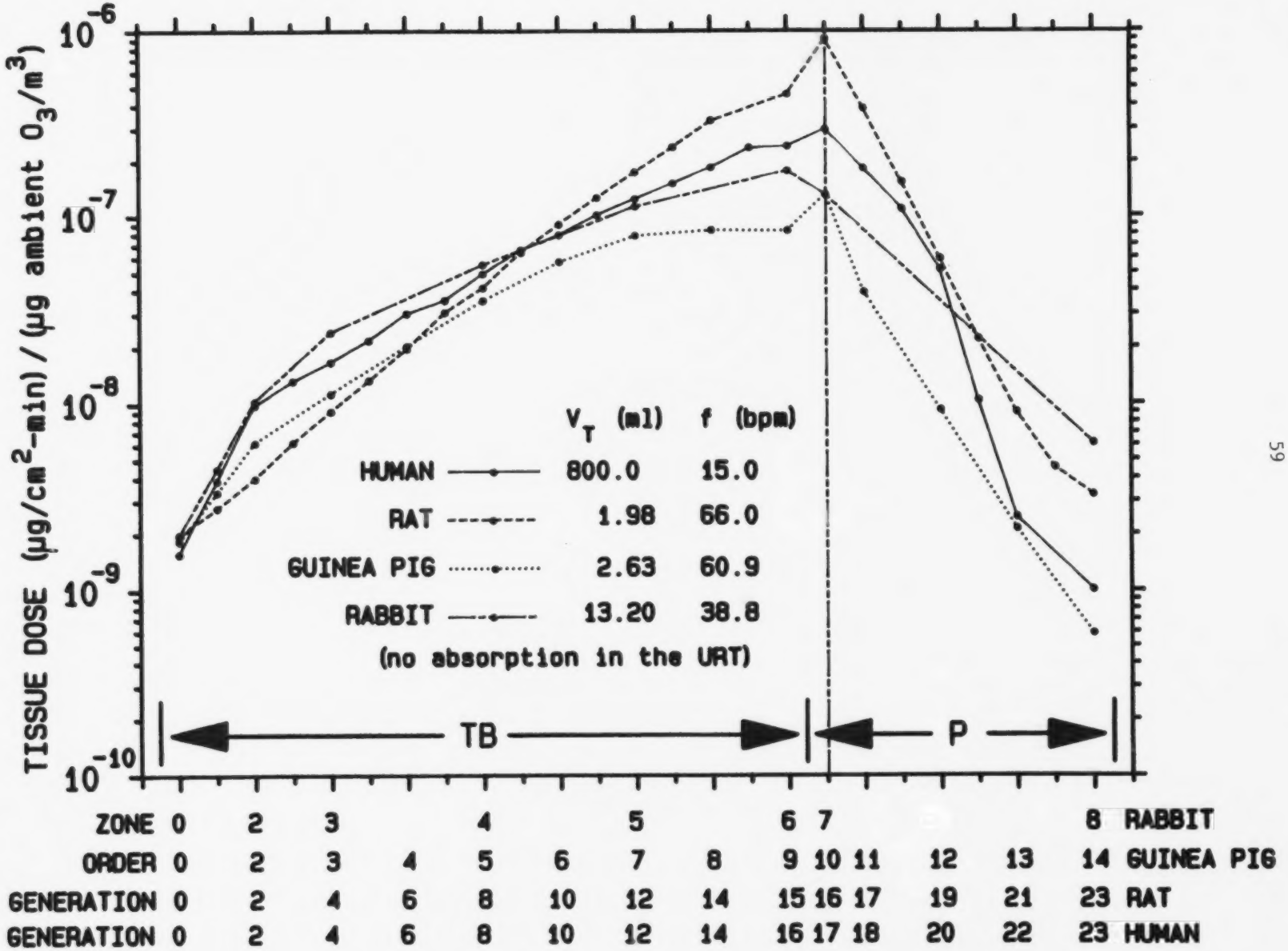
2


A
B
C
D
NET
TISSUE
TB
P
NORMALIZED DOSE (μg/cm²–minute)/(μg tracheal O₃/m³)
ZONE
ORDER
GENERATION


10-7
10-8
10-9
10-10
10-11
DOSE (μg/cm2-breath)/(μg Tracheal O3/m3)
A'
C'
B'
B
A
C
0
4
8
12
16
20
AIRWAY GENERATION (Z)
TB
P


NET DOSE (µg/cm²-min) / (µg ambient O₃/m³)
10⁻⁶
10⁻⁷
10⁻⁸
10⁻⁹
10⁻¹⁰
V_T (ml) f (bpm)
HUMAN 800.0 15.0
RAT 1.98 66.0
GUINEA PIG 2.63 60.9
RABBIT 13.20 38.8
(no absorption in the URT)
TB
P
ZONE 0 2 3 4 5 6 7 8 RABBIT
ORDER 0 2 3 4 5 6 7 8 9 10 11 12 13 14 GUINEA PIG
GENERATION 0 2 4 6 8 10 12 14 15 16 17 19 21 23 RAT
GENERATION 0 2 4 6 8 10 12 14 16 17 18 20 22 23 HUMAN

5A


TISSUE DOSE (μg/cm²-min) / (μg ambient O₃/m³)
10⁻⁶
10⁻⁷
10⁻⁸
10⁻⁹
10⁻¹⁰
V_T (ml) f (bpm)
HUMAN 800.0 15.0
RAT 1.98 66.0
GUINEA PIG 2.63 60.9
RABBIT 13.20 38.8
(no absorption in the URT)
TB
P
ZONE 0 2 3 4 5 6 7 8 RABBIT
ORDER 0 2 3 4 5 6 7 8 9 10 11 12 13 14 GUINEA PIG
GENERATION 0 2 4 6 8 10 12 14 15 16 17 19 21 23 RAT
GENERATION 0 2 4 6 8 10 12 14 16 17 18 20 22 23 HUMAN